IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: **Eric J. Benjamin, *et al.***	Confirmation No.: **7245**
Application No.: **10/820,215**	Group Art Unit: **1624**
Filing Date: **April 7, 2004**	Examiner: **Brenda Libby Coleman**

For: **Pharmaceutical Compositions for Intranasal Administration of [2-(8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)alkyl] Phosphonic Acid and Derivatives and Methods of Use Thereof**

Mail Stop Appeal Brief -- Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

APPELLANTS' REPLY BRIEF PURSUANT TO 37 C.F.R. § 41.41

Appellants submit this Reply in response to the Examiner's Answer dated October 10, 2007 in connection with the above-identified application.[1] This reply is being filed within two months of the Examiner's Answer dated October 10, 2007. An Appeal Brief was timely filed on May 21, 2007 in support of Appellants' appeal from the final rejection of claims 1 to 56 mailed November 22, 2006. A Notice of Appeal was timely filed on March 21, 2007. Appellants are submitting herewith a Request for Oral Arguments and requisite fee.

[1]A first Examiner's Answer was issued on September 6, 2007. However, a second, revised Examiner's Answer dated October 10, 2007 was then issued on October 10, 2007. This Reply Brief addresses the issues raised in these documents.

1. REAL PARTY IN INTEREST

The real party in interest is Wyeth, Five Giralda Farms, Madison, New Jersey 07940.

2. RELATED APPEALS AND INTERFERENCES

No related appeals or interferences are pending. See appendix entitled RELATED PROCEEDINGS APPENDIX.

3. STATUS OF CLAIMS

Pending	:	Claims 1 to 56
Rejected	:	Claims 1 to 56
Objected to	:	None
Allowed	:	None
Withdrawn	:	None
Appealed	:	Claims 1 to 56.

The appealed claims are listed in the appendix entitled CLAIMS APPENDIX.

4. STATUS OF AMENDMENTS

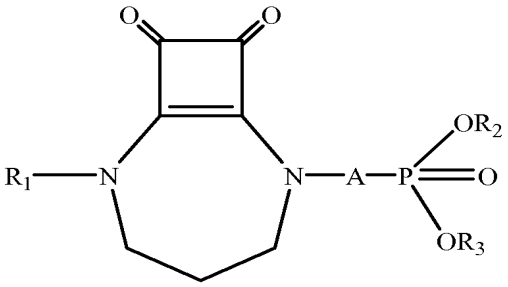
The amendments to claims 27, 33, and 55 filed subsequent to Final Rejection were entered.

5. SUMMARY OF CLAIMED SUBJECT MATTER

The present invention provides pharmaceutical compositions and methods for treating conditions associated with glutamate abnormalities, *i.e.,* conditions produced by a disease or a disorder in which glutamate, typically in increased amounts, is implicated as a contributing factor, by administering the pharmaceutical compositions.

Independent claim 1 is directed to pharmaceutical compositions for intranasal administration comprising:

a) a therapeutically effective amount of at least one compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R_1 is hydrogen;

A is $-(CH_2)_n-$, where n is 2; and

R_2 and R_3 are hydrogen; and

b) one or more pharmaceutically acceptable additives for forming a composition for intranasal administration.

See specification, page 5, line 15 to page 6, line 18; page 8, line 13 to page 9, line 10.

Claim 10 is directed to methods for treating at least one condition in a mammal selected from a cerebral vascular disorder selected from cerebral ischemia, cerebral infarction or cerebral vasospasm; cerebral trauma; muscular spasm; a convulsive disorder selected from epilepsy or status epilepticus; hypoglycemia; cardiac arrest; asphyxia anoxia; or spinal chord injury comprising administering intranasally to a mammal in need thereof a therapeutically effective amount of the composition of claim 1.

See specification, page 19, line 9 to page 20, line 4.

Claim 12 is directed to methods for treating at least one condition in a mammal selected from glaucoma or diabetic end organ complications comprising administering intranasally to a mammal in need thereof a therapeutically effective amount of the composition of claim 1.

See specification, page 19, line 9 to page 20, line 4.

Claim 13 is directed to methods for treating at least one condition in a mammal selected from anxiety disorders; mood disorders; schizophrenia; schizophreniform disorder; or schizoaffective disorder comprising intranasally administering to a mammal in need thereof a therapeutically effective amount of the composition of claim 1.

See specification, page 19, line 9 to page 20, line 4.

Claim 16 is directed to methods for treating at least one neurodegenerative disorder in a mammal selected from Huntingdon's disease, alzheimer's disease, amyotrophic lateral sclerosis, chronic dementia, or cognitive impairment comprising intranasally administering to a mammal in need thereof a therapeutically effective amount of the composition of claim 1.

See specification, page 19, line 9 to page 20, line 4.

Claim 18 is directed to methods for treating Parkinson's disease comprising intranasally administering to a mammal in need thereof a therapeutically effective amount of the composition of claim 1.

See specification, page 19, line 9 to page 20, line 4.

Claim 20 is directed to methods for treating at least one condition in a mammal selected from inflammatory diseases; fibromyalgia; complications from herpes zoster; prevention of tolerance to opiate analgesia; or withdrawal symptoms from addictive drugs comprising intranasally administering to a mammal in need thereof a therapeutically effective amount of the composition of claim 1.

See specification, page 20, lines 5 to 15.

Claim 21 is directed to methods for treating pain in a mammal comprising administering intranasally to a mammal in need thereof a therapeutically effective amount of the composition of claim 1.

See specification, page 20, line 16 to page 22, line 12.

Claim 26 is directed to pharmaceutical compositions for intranasal administration, in unit dosage or multiple dose form, comprising:

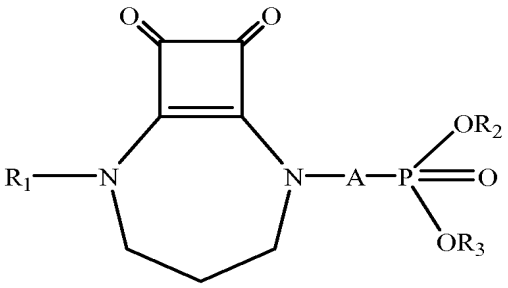
a) a therapeutically effective unit dosage or multiple dose for intranasal administration of [2-(8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)ethyl] phosphonic acid; and

b) one or more pharmaceutically acceptable additives for forming a composition for intranasal administration.

See specification, page 18, line 26 to page 19, line 8; page 22, lines 13 to 18.

Claim 27 is directed to pharmaceutical compositions for intranasal administration comprising:

a) a therapeutically effective amount of at least one compound of formula (I) or a pharmaceutically acceptable salt thereof:



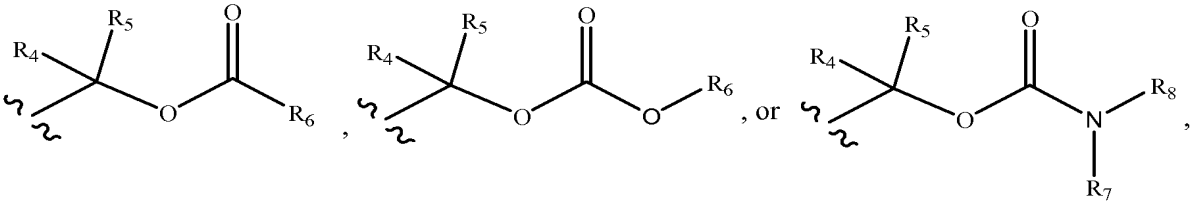
(I)

wherein:

R_1 is hydrogen, a C_1 to C_6 alkyl group, a C_2 to C_7 acyl group, a C_1 to C_6 alkanesulfonyl group, or a C_6 to C_{14} aroyl group;

A is alkylene of 1 to 4 carbon atoms or alkenylene of 2 to 4 carbon atoms;

R_2 and R_3 are independently selected from hydrogen, or



with the proviso that at least one of R_2 and R_3 is not hydrogen;

R_4 and R_5 are independently selected from hydrogen, a C_1 to C_4 alkyl group, a C_5 to C_7 aryl group, a C_6 to C_{15} alkylaryl group having 5 to 7 carbon atoms in the aryl ring, a C_2 to C_7 alkenyl group, or C_2 to C_7 alkynyl group, or R_4 and R_5 may together form a spiro C_3 to C_8 carbocyclic ring;

R_6 is a C_1 to C_{12} linear or branched alkyl group, a C_2 to C_7 linear or branched alkenyl or alkynyl group, a C_5 to C_{13} aryl group, a C_6 to C_{21} alkylaryl group having 5 to 13 carbon atoms in the aryl moiety; a 5 to 13 membered heteroaryl group, a 6 to 21 membered alkylheteroaryl group having 5 to 13 members in the heteroaryl moiety, a C_4 to C_8 cycloalkyl group, a C_5 to C_{16} alkylcycloalkyl group having 4 to 8 carbon atoms in the cycloalkyl ring;

R_7 and R_8 are independently selected from hydrogen, a C_1 to C_{12} linear or branched alkyl group, a C_2 to C_7 linear or branched alkenyl or alkynyl group, a C_5 to C_{13} aryl group, a C_6 to C_{21} alkylaryl group having 5 to 13 carbon atoms in the aryl moiety, a 5 to 13 membered heteroaryl group, a 6 to 21 membered alkylheteroaryl group having 5 to 13 members in the heteroaryl moiety, or R_7 and R_8 may together form a cycloalkyl or heterocycloalkyl group having in the ring 4 to 8 carbon atoms and optionally one to two atoms selected from nitrogen, oxygen or sulfur;

wherein any R_1 to R_8 group having an aryl, heteroaryl, cycloalkyl or heterocycloalkyl moiety may optionally be substituted on the aryl, heteroaryl, cycloalkyl or heterocycloalkyl moiety with 1 to about 5 substituents independently selected from a halogen atom, a cyano, nitro or hydroxyl group, a C_1-C_6 alkyl group, or a C_1-C_6 alkoxy group; and

b) one or more pharmaceutically acceptable additives for forming a composition for intranasal administration.

See specification, page 5, line 15 to page 19, line 8.

Claim 42 is directed to methods for treating at least one condition in a mammal selected from a cerebral vascular disorder selected from cerebral ischemia, cerebral infarction or cerebral vasospasm; cerebral trauma; muscular spasm; a convulsive disorder selected from

epilepsy or status epilepticus; glaucoma; diabetic end organ complications; hypoglycemia; cardiac arrest; asphyxia anoxia; or spinal chord injury comprising administering intranasally to a mammal in need thereof a therapeutically effective amount of the composition of claim 27.

See specification, page 19, line 9 to page 20, line 4.

Claim 44 is directed to methods for treating at least one condition in a mammal selected from anxiety disorders; mood disorders; schizophrenia; schizophreniform disorder; or schizoaffective disorder comprising intranasally administering to a mammal in need thereof a therapeutically effective amount of the composition of claim 27.

See specification, page 19, line 9 to page 20, line 4.

Claim 47 is directed to methods for treating at least one neurodegenerative disorder in a mammal selected from Parkinson's disease, Huntingdon's disease, alzheimer's disease, amyotrophic lateral sclerosis, chronic dementia, or cognitive impairment comprising intranasally administering to a mammal in need thereof a therapeutically effective amount of the composition of claim 27.

See specification, page 19, line 9 to page 20, line 4.

Claim 49 is directed to methods for treating at least one condition in a mammal selected from inflammatory diseases; fibromyalgia; complications from herpes zoster; prevention of tolerance to opiate analgesia; or withdrawal symptoms from addictive drugs comprising intranasally administering to a mammal in need thereof a therapeutically effective amount of the composition of claim 27.

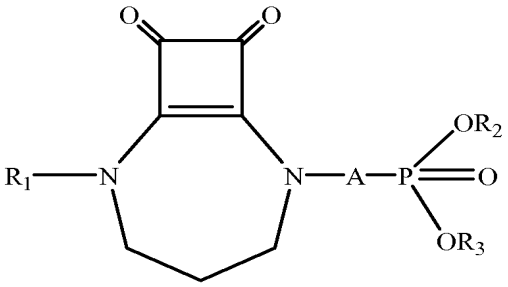
See specification, page 19, line 9 to page 20, line 4.

Claim 50 is directed to methods for treating pain in a mammal comprising administering intranasally to a mammal in need thereof a therapeutically effective amount of the composition of claim 27.

See specification, page 20, line 16 to page 22, line 12.

Claim 55 is directed to pharmaceutical compositions for intranasal administration, in unit dosage or multiple dose form, comprising:

a) a therapeutically effective unit dosage or multiple dose for intranasal administration of at least one compound of formula (I) or a pharmaceutically acceptable salt thereof:



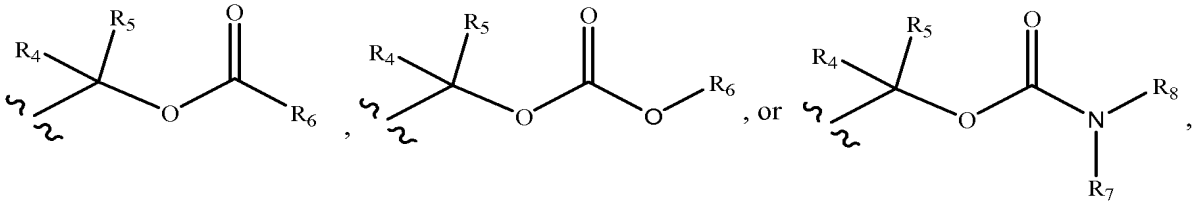
(I)

wherein:

R_1 is hydrogen, a C_1 to C_6 alkyl group, a C_2 to C_7 acyl group, a C_1 to C_6 alkanesulfonyl group, or a C_6 to C_{14} aroyl group;

A is alkylene of 1 to 4 carbon atoms or alkenylene of 2 to 4 carbon atoms;

R_2 and R_3 are independently selected from hydrogen, or



with the proviso that at least one of R_2 and R_3 is not hydrogen;

R_4 and R_5 are independently selected from hydrogen, a C_1 to C_4 alkyl group, a C_5 to C_7 aryl group, a C_6 to C_{15} alkylaryl group having 5 to 7 carbon atoms in the aryl ring, a C_2 to C_7 alkenyl group, or C_2 to C_7 alkynyl group, or R_4 and R_5 may together form a spiro C_3 to C_8 carbocyclic ring;

R_6 is a C_1 to C_{12} linear or branched alkyl group, a C_2 to C_7 linear or branched alkenyl or alkynyl group, a C_5 to C_{13} aryl group, a C_6 to C_{21} alkylaryl group having 5 to 13 carbon atoms in the aryl moiety; a 5 to 13 membered heteroaryl group, a 6 to 21 membered alkylheteroaryl group having 5 to 13 members in the heteroaryl moiety, a C_4 to C_8 cycloalkyl group, a C_5 to C_{16} alkylcycloalkyl group having 4 to 8 carbon atoms in the cycloalkyl ring;

R_7 and R_8 are independently selected from hydrogen, a C_1 to C_{12} linear or branched alkyl group, a C_2 to C_7 linear or branched alkenyl or alkynyl group, a C_5 to C_{13} aryl group, a C_6 to C_{21} alkylaryl group having 5 to 13 carbon atoms in the aryl moiety, a 5 to 13 membered heteroaryl group, a 6 to 21 membered alkylheteroaryl group having 5 to 13 members in the heteroaryl moiety, or R_7 and R_8 may together form a cycloalkyl or heterocycloalkyl group having in the ring 4 to 8 carbon atoms and optionally one to two atoms selected from nitrogen, oxygen or sulfur;

wherein any R_1 to R_8 group having an aryl, heteroaryl, cycloalkyl or heterocycloalkyl moiety may optionally be substituted on the aryl, heteroaryl, cycloalkyl or heterocycloalkyl moiety with 1 to about 5 substituents independently selected from a halogen atom, a cyano, nitro or hydroxyl group, a C_1-C_6 alkyl group, or a C_1-C_6 alkoxy group; and

b) one or more pharmaceutically acceptable additives for forming a composition for intranasal administration.

See specification, page 18, line 26 to page 19, line 8; page 22, lines 13 to 18.

6. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

There are three issues in this appeal:

A. Whether claims 1 to 56 are enabled under 35 U.S.C. § 112, first paragraph;

B. Whether claims 25 and 54 are indefinite under 35 U.S.C. § 112, second paragraph; and

C. Whether claims 1 to 26 are anticipated by EP-A-0,778,023 under 35 U.S.C. § 102(b).

7. ARGUMENTS

Provisional Obviousness-type Double Patenting

Appellants acknowledge, as noted in the Examiner's Answer of October 10, 2007, that certain appealed claims are provisionally rejected for obviousness-type double patenting. More specifically, claims 1 to 9 and 26 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 26 to 29 of US 10/969,715. Claims 27 to 55 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 11 to 28 of US 10/820,216. Claims 27 to 56 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 1 to 95 and 104 to 108 of US 10/961,871. Finally, claims 21 to 24 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 37 to 53 and 57 to 73 of US 10/267,159.

However, since these rejections are provisional, appellants request that they be held in abeyance until the identification of otherwise allowable subject matter, wherein appellants will consider the propriety of filing one or more terminal disclaimers to obviate the rejections.

Claims 1 to 56 are enabled

Appellants submit that claims 1 to 56 directed to both pharmaceutical compositions and methods of treatments using these pharmaceutical compositions are enabled under 35 U.S.C. § 112, first paragraph. Appellants have shown that there is a ***nexus*** between NMDA antagonists and the treatment of the diseases and/or disorders listed in the claims to support enablement of claims 1 to 56. Further, appellants submit that the claims are enabled with respect to the ***prevention*** of opiate tolerance.

With respect to the enablement of the prevention of disorders, the Office is in error and has presented no evidence why there is any reason to believe that a skilled artisan would doubt that the compounds of the invention would not be useful in preventing opiate tolerance, especially in light of the fact that NMDA receptor antagonists are known to prevent the opiate analgesia tolerance. See, for example, the Trujillo abstract (provided in EVIDENCE APPENDIX). Contrary to the allegations made by the Office, this abstract indicates that a decade of research establishes that "NMDA receptor antagonists have the ability to inhibit opiate tolerance," even if the exact mode of action is not known. (Trujillo abstract, lines 1 to 2). Furthermore, medical professionals have means to measure tolerance to opiate analgesia and would have no difficulty administering the compounds of the invention to effect the desired result, *i.e.*, prevention of the tolerance. No other evidence has been presented that

establishes that a skilled artisan would doubt the use of the compounds of the invention, which are NMDA receptor antagonists, would not be useful in the treatment of the listed diseases and conditions.

Appellants submit that the pharmaceutical composition claims meet the enablement requirements under 35 U.S.C. § 112, first paragraph. Appellants have described in sufficient detail to enable a person ordinary skilled in the art to make and use the intranasal compositions without undue experimentation. For example, appellants provide a description of the synthesis of the active compound on page 12, line 8 to page 14, line 3, three actual examples of how to formulate the intranasal compositions (Examples 1 to 3), and they also describe how other types of intranasal may be prepared on page 14, line 4 to page 19, line 8. Thus, appellants submit that the composition claims are enabled.

Further, appellants submit that the method of treatment claims also meet the enablement requirements under 35 U.S.C. § 112, first paragraph. With the exception of cerebral ischemia, it appears that the Office is challenging that there is a correlation between antagonists of the NMDA receptor and the treatment of the various diseases and conditions claimed. As appellants explained on page 14, line 8 to page 15, line 11, the present invention provides methods for treating conditions associated with glutamate abnormalities, *i.e.,* conditions produced by a disease or a disorder in which glutamate, typically in increased amounts, is implicated as a contributing factor. The Office has provided no evidence that any of the listed conditions would not be expected to be treated by the compounds of the invention. A rigorous or an invariable exact correlation is not required, as stated in *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985):

> based upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed *in vitro* utility and *in vivo* activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonably based upon the probative evidence. (citations omitted).

Appellant previously submitted a number of review articles and have included these in the EVIDENCE APPENDIX that show that there is recognized correlation between antagonism at the NMDA receptors and the specified diseases and conditions set forth in the claims:

- Wood PL.
  The NMDA receptor complex: a long and winding road to therapeutics.
  Drugs. 2005 Mar;8(3):229-35. Review.

- Heresco-Levy U.
  Glutamatergic neurotransmission modulators as emerging new drugs for schizophrenia.
  Expert Opin Emerg Drugs. 2005 Nov;10(4):827-44. Review.

- Bergink V, van Megen HJ, Westenberg HG.
  Glutamate and anxiety.
  Eur. Neuropsychopharmacol. 2004 May;14(3):175-83. Review.

- Parsons CG.
  NMDA receptors as targets for drug action in neuropathic pain.
  Eur J Pharmacol. 2001 Oct 19;429(1-3):71-8. Review.

- Brown DG, Krupp JJ.
  N-methyl-D-aspartate receptor (NMDA) antagonists as potential pain therapeutics.
  Curr Top Med Chem. 2006;6(8):749-70

- McCulloch J.
  Excitatory amino acid antagonists and their potential for the treatment of ischaemic brain damage in man.
  Br J Clin Pharmacol. 1992 Aug;34(2):106-14. Review.

Appellants acknowledge that some of the review articles are not prior art references themselves because of their publication dates, but they review prior art that establishes the

correlation between antagonism at the NMDA receptors and the specified diseases and conditions set forth in the claims.

Appellants have demonstrated that compounds useful in the intranasal compositions of the invention, NMDA receptor antagonists through testing in the art-recognized *in vivo* prostaglandin E_2-induced thermal hypersensitivity test. See, Example 30 in the specification, page 30, line 19 to page 33, line 9. If the prior art is such a particular model is recognized as correlating to a specific condition, then it should be accepted by the Office as correlating unless the Office has evidence that the model does not correlate. Even with such evidence, the Office must weight the evidence for and against such correlation and determine whether a skilled artisan would accept the model as reasonably correlating to the condition. *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995)(reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications). Appellants submit that the Office has not met this burden.

Accordingly, appellants submit that claims 1 to 56 meet the enablement requirement under 35 U.S.C. § 112, second paragraph, and therefore request withdrawal of the rejection.

Claims 25 and 54 are definite

Appellants submit that claims 25 and 54, which use the phrase "pain relieving agent" are definite under 35 U.S.C. § 112, second paragraph.

Appellants submit that a skilled artisan would have no difficulty understanding the meaning of the phrase "pain relieving agent." Furthermore, on page 23, lines 22 to 25 and

page 24, lines 10 to 25, appellants have provided numerous specific examples of pain relieving agents, leaving no doubt with the skilled artisan to the metes and bounds of the invention with respect to the pain relieving agents.

Accordingly, appellants submit that claims 25 and 54 meet the definiteness requirement under 35 U.S.C. § 112, second paragraph, and therefore request withdrawal of the rejection.

Claims 1 to 26 are not anticipated by EP-A-0,778,023

Appellants submit that claims 1 to 26 are novel over EP-A-0,778,023 under 35 U.S.C. § 102(b). Composition claims 1 to 9 require an excipient for intranasal administration and method claims 10 to 26 require that the composition of claim 1 be administered intranasally. It is the Office's position that because EP-B1-0,778,023 discloses that rapamycin may be administered intranasally in **[0029]** and because it also discloses that the product contains an NMDA antagonist such as [2-(8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)ethyl] phosphonic acid (EAA-090), it necessarily discloses that the EAA-090 is administered intranasally thereby anticipating claims 1 to 26. Appellants disagree because EP-B1-0,778,023 never discloses a product containing both rapamycin and EAA-090 that is administered intranasally.

While EP-B1-0,778,023 discloses that the rapamycin may be administered intranasally, it further indicates that the NMDA antagonist does not necessarily need to administered at the same time. See **[0008]**. Even if the rapamycin and the NMDA antagonist are administered at the same time, this does not necessarily require that the compounds

administered in the same manner. Importantly, EP-B1-0,778,023 is silent with respect to intranasal administration of compositions of the NMDA antagonists and such route of administration is not inherent in the disclosure. The missing descriptive matter is not necessarily present in the thing described in the reference. "Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1269, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991)(quoting *In re Oelrich*, 666 F.2d 578, 581, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981); *Ex parte Skinner*, 2 USPQ 2d 1788, 1789 (B.P.A.I. 1986). (*See also* M.P.E.P. §2112 (IV)). The inherent feature must *necessarily* lead one skilled in the art to the claimed subject matter. *Hyatt v. Boone*, 146 F.3d 1348, 47 USPQ.2d 1128 (Fed. Cir. 1998). *Kennecott Corporation v. Kyocera International, Inc. and Kyoto Ceramic Co., Ltd.*, 835 F.2d 1419, 5 USPQ.2d 1194 (Fed. Cir. 1987). The fact that intranasal administration of both the rapamycin and EAA-090 might have been carried out is insufficient.

Since EP-B1-0,778,023 does not disclose each and every element of the claim either explicitly or inherently, EP-B1-0,778,023 does not anticipate claims 1 to 56. Accordingly, appellants request withdrawal of the rejection under 35 U.S.C. § 102(b) over EP-B1-0,778,023.

Conclusions

For the foregoing reasons, it is respectfully submitted that claims 1 to 56 are enabled, definite, and novel. Appellants, therefore, request that this patent application be remanded to the Patent Office with an instruction to withdraw the rejections of the claims of the appealed claims.

Respectfully submitted,

Date: **November 6, 2007**

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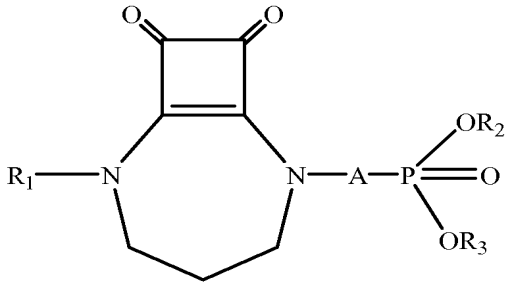
CLAIMS APPENDIX

The following claims are involved in the present appeal:

1. A pharmaceutical composition for intranasal administration comprising:

a) a therapeutically effective amount of at least one compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R_1 is hydrogen;

A is $-(CH_2)_n-$, where n is 2; and

R_2 and R_3 are hydrogen; and

b) one or more pharmaceutically acceptable additives for forming a composition for intranasal administration.

2. The composition of claim 1 wherein the composition has a pH ranging from about 3 to about 9.

3. The composition of claim 1 wherein the pharmaceutically acceptable additives comprise at least one additive selected from liquid or solid carriers; absorbance

enhancers; pH adjusting agents; metal chelating agents; buffers; thickening agents; humectants; or bioadhesives or combinations thereof.

4. The composition of claim 3 wherein the pharmaceutically acceptable additives are present in the composition in an amount of from about 0.25 to about 95 weight percent, based on the total weight of the composition.

5. The composition of claim 1 wherein the composition is in the form of a liquid selected from a solution, gel, suspension, dispersion or emulsion.

6. The composition of claim 5 wherein the compound of formula (I) is present in the composition in an amount of from about 50 mg/ml to about 300 mg/ml.

7. The composition of claim 1 wherein the composition is in the form of a powder.

8. The composition of claim 7 wherein the powder has a particle size of less than about 250 microns.

9. The composition of claim 8 wherein the powder has a particle size of less than about 180 microns.

10. A method for treating at least one condition in a mammal selected from a cerebral vascular disorder selected from cerebral ischemia, cerebral infarction or cerebral vasospasm; cerebral trauma; muscular spasm; a convulsive disorder selected from epilepsy or status epilepticus; hypoglycemia; cardiac arrest; asphyxia anoxia; or spinal

chord injury comprising administering intranasally to a mammal in need thereof a therapeutically effective amount of the composition of claim 1.

11. The method of claim 10 wherein the mammal is human.

12. A method for treating at least one condition in a mammal selected from glaucoma or diabetic end organ complications comprising administering intranasally to a mammal in need thereof a therapeutically effective amount of the composition of claim 1.

13. A method for treating at least one condition in a mammal selected from anxiety disorders; mood disorders; schizophrenia; schizophreniform disorder; or schizoaffective disorder comprising intranasally administering to a mammal in need thereof a therapeutically effective amount of the composition of claim 1.

14. The method of claim 13 wherein the anxiety disorder is selected from panic attack, agoraphobia, panic disorder, specific phobia, social phobia, obsessive compulsive disorder, posttraumatic stress disorder, acute stress disorder, generalized anxiety disorder, separation anxiety disorder, or substance-induced anxiety disorder; or the mood disorder is selected from bipolar disorders, depressive disorders selected from major depressive disorder, dysthymic disorder, or substance-induced mood disorder, or mood episodes selected from major depressive episode, manic episode, mixed episode, or hypomanic episode.

15. The method of claim 13 wherein the mammal is human.

16. A method for treating at least one neurodegenerative disorder in a mammal selected from Huntingdon's disease, alzheimer's disease, amyotrophic lateral sclerosis, chronic dementia, or cognitive impairment comprising intranasally administering to a mammal in need thereof a therapeutically effective amount of the composition of claim 1.

17. The method of claim 16 wherein the mammal is a human.

18. A method for treating Parkinson's disease comprising intranasally administering to a mammal in need thereof a therapeutically effective amount of the composition of claim 1.

19. The method of claim 18 wherein the mammal is a human.

20. A method for treating at least one condition in a mammal selected from inflammatory diseases; fibromyalgia; complications from herpes zoster; prevention of tolerance to opiate analgesia; or withdrawal symptoms from addictive drugs comprising intranasally administering to a mammal in need thereof a therapeutically effective amount of the composition of claim 1.

21. A method for treating pain in a mammal comprising administering intranasally to a mammal in need thereof a therapeutically effective amount of the composition of claim 1.

22. The method of claim 21 wherein the pain is at least one of neuropathic pain; cancer pain; visceral pain associated with pancreatitis or abdominal, pelvic or perineal regions; musculoskeletal pain associated with lower or upper back, spine, fibromylagia, temporomandibular joint, or myofascial pain syndrome; bony pain associated with bone or joint degenerating disorders; headaches; or pain associated with infections, sickle cell anemia, autoimmune disorders, multiple sclerosis, dental procedures, burns or inflammation.

23. The method of claim 21 wherein the mammal is human.

24. The method of claim 21 wherein the pain comprises neuropathic pain and is associated with at least one of diabetic neuropathy, peripheral neuropathy, post-herpetic neuralgia, trigeminal neuralgia, lumbar or cervical radiculopathies, fibromyalgia, glossopharyngeal neuralgia, reflex sympathetic dystrophy, casualgia, thalamic syndrome, nerve root avulsion, or nerve damage cause by injury selected from phantom limb pain, reflex sympathetic dystrophy or postthoracotomy pain, cancer, chemical injury, toxins, nutritional deficiencies, or viral or bacterial infections.

25. The method of claim 21 further comprising administering a therapeutically effective amount of at least one pain relieving agent.

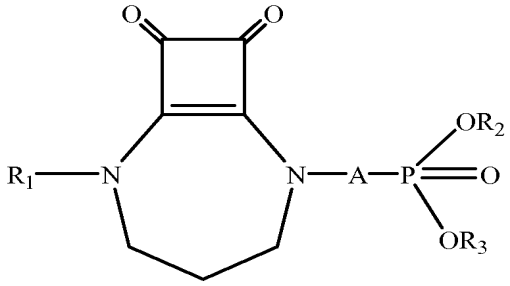
26. A pharmaceutical composition for intranasal administration, in unit dosage or multiple dose form, comprising:

a) a therapeutically effective unit dosage or multiple dose for intranasal administration of [2-(8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)ethyl] phosphonic acid; and

b) one or more pharmaceutically acceptable additives for forming a composition for intranasal administration.

27. A pharmaceutical composition for intranasal administration comprising:

a) a therapeutically effective amount of at least one compound of formula (I) or a pharmaceutically acceptable salt thereof:



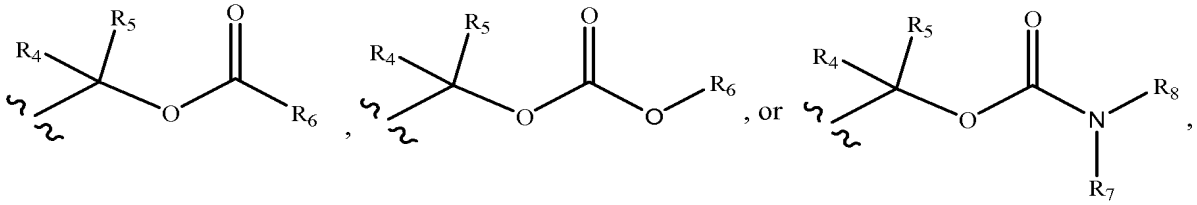
(I)

wherein:

R_1 is hydrogen, a C_1 to C_6 alkyl group, a C_2 to C_7 acyl group, a C_1 to C_6 alkanesulfonyl group, or a C_6 to C_{14} aroyl group;

A is alkylene of 1 to 4 carbon atoms or alkenylene of 2 to 4 carbon atoms;

R_2 and R_3 are independently selected from hydrogen, or



with the proviso that at least one of R_2 and R_3 is not hydrogen;

R_4 and R_5 are independently selected from hydrogen, a C_1 to C_4 alkyl group, a C_5 to C_7 aryl group, a C_6 to C_{15} alkylaryl group having 5 to 7 carbon atoms in the aryl ring, a C_2 to C_7 alkenyl group, or C_2 to C_7 alkynyl group, or R_4 and R_5 may together form a spiro C_3 to C_8 carbocyclic ring;

R_6 is a C_1 to C_{12} linear or branched alkyl group, a C_2 to C_7 linear or branched alkenyl or alkynyl group, a C_5 to C_{13} aryl group, a C_6 to C_{21} alkylaryl group having 5 to 13 carbon atoms in the aryl moiety; a 5 to 13 membered heteroaryl group, a 6 to 21 membered alkylheteroaryl group having 5 to 13 members in the heteroaryl moiety, a C_4 to C_8 cycloalkyl group, a C_5 to C_{16} alkylcycloalkyl group having 4 to 8 carbon atoms in the cycloalkyl ring;

R_7 and R_8 are independently selected from hydrogen, a C_1 to C_{12} linear or branched alkyl group, a C_2 to C_7 linear or branched alkenyl or alkynyl group, a C_5 to C_{13} aryl group, a C_6 to C_{21} alkylaryl group having 5 to 13 carbon atoms in the aryl moiety, a 5 to 13 membered heteroaryl group, a 6 to 21 membered alkylheteroaryl group having 5 to 13 members in the heteroaryl moiety, or R_7 and R_8 may together form a cycloalkyl or heterocycloalkyl group having in the ring 4 to 8 carbon atoms and optionally one to two atoms selected from nitrogen, oxygen or sulfur;

wherein any R_1 to R_8 group having an aryl, heteroaryl, cycloalkyl or heterocycloalkyl moiety may optionally be substituted on the aryl, heteroaryl, cycloalkyl or heterocycloalkyl moiety with 1 to about 5 substituents independently selected from a halogen atom, a cyano, nitro or hydroxyl group, a C_1-C_6 alkyl group, or a C_1-C_6 alkoxy group; and

b) one or more pharmaceutically acceptable additives for forming a composition for intranasal administration.

28. The composition of claim 27 wherein R_1 is H.

29. The composition of claim 28 wherein A is an alkylene group having the formula -$(CH_2)_n$-, where n is 1 to 3.

30. The composition of claim 29 wherein n is 2.

31. The composition of claim 30 wherein R_4 and R_5 are independently selected from H or a C_1 to C_4 alkyl group, and R_6 is selected from a C_3 to C_{10} linear or branched alkyl group, a C_5 to C_7 aryl group, a 5- to 7-membered heteroaryl group, or a cycloalkyl group having in the ring 5 to 7 carbon atoms.

32. The composition of claim 31 wherein R_6 is a C_5 to C_7 aryl group.

33. The composition of claim 27 wherein at least one compound of formula (I) is selected from:

a) 3-{2-[8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl]ethyl}-3-oxido-7-oxo-7-phenyl-2,4,6-trioxa-3-phosphahept-1-yl benzoate;

b) 3-{2-[8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl]ethyl}-3-oxido-7-oxo-8-propyl-2,4,6-trioxa-3-phosphaundec-1-yl-2-propylpentanoate;

c) 2,2-dimethyl-propionic acid {(2,2-dimethyl-propionyloxymethoxy)-[2-(8,9-dioxo-2,6-diaza-bicyclo[5.2.0]-non-1(7)-en-2-yl)-ethyl]-phosphinoyloxy} methyl ester;

d) 7-cyclohexyl-3-{2-[8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl]ethyl}-1,5-dimethyl-3-oxido-7-oxo-2,4,6-trioxa-3-phosphahept-1-yl cyclohexanecarboxylate;

e) 7-cyclohexyl-3-{2-[8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl]ethyl}-3-oxido-7-oxo-2,4,6-trioxa-3-phosphahept-1-yl cyclohexanecarboxylate;

f) [2-(8,9-Dioxo-2,6-diaza-bicyclo[5.2.0]non-1-(7)-en-2-yl)-ethyl]-phosphonic acid diisopropoxycarbonyl oxymethyl ester;

g) [2-[8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl]ethyl]-phosphonic acid bis[1-(benzoyloxy)ethyl] ester;

h) benzoic acid [2-(8,9-dioxo-2,6-diaza-bicyclo[5.2.0]non-1(7)-en-2-yl)-ethyl]-hydroxy-phosphinoyloxymethyl ester; or

i) [2-(8,9-Dioxo-2,6-diaza-bicyclo[5.2.0]non-1(7)-en-2-yl)-ethyl]-phosphonic acid di-dimethylcarbamoyloxymethyl ester; or

a pharmaceutically acceptable salt thereof.

34. The composition of claim 27 wherein the composition has a pH ranging from about 3 to about 9.

35. The composition of claim 27 wherein the pharmaceutically acceptable additives comprise at least one additive selected from liquid or solid carriers; absorbance enhancers; pH adjusting agents; metal chelating agents; buffers; thickening agents; humectants; or bioadhesives or combinations thereof.

36. The composition of claim 35 wherein the pharmaceutically acceptable additives are present in the composition in an amount of from about 0.25 to about 95 weight percent, based on the total weight of the composition.

37. The composition of claim 27 wherein the composition is in the form of a liquid selected from a solution, gel, suspension, dispersion or emulsion.

38. The composition of claim 37 wherein the compound of formula (I) is present in the composition in an amount of from about 50 mg/ml to about 300 mg/ml.

39. The composition of claim 27 wherein the composition is in the form of a powder.

40. The composition of claim 39 wherein the powder has a particle size of less than about 250 microns.

41. The composition of claim 40 wherein the powder has a particle size of less than about 180 microns.

42. A method for treating at least one condition in a mammal selected from a cerebral vascular disorder selected from cerebral ischemia, cerebral infarction or cerebral vasospasm; cerebral trauma; muscular spasm; a convulsive disorder selected from epilepsy or status epilepticus; glaucoma; diabetic end organ complications; hypoglycemia; cardiac arrest; asphyxia anoxia; or spinal chord injury comprising administering intranasally to a mammal in need thereof a therapeutically effective amount of the composition of claim 27.

43. The method of claim 42 wherein the mammal is human.

44. A method for treating at least one condition in a mammal selected from anxiety disorders; mood disorders; schizophrenia; schizophreniform disorder; or schizoaffective disorder comprising intranasally administering to a mammal in need thereof a therapeutically effective amount of the composition of claim 27.

45. The method of claim 44 wherein the anxiety disorder is selected from panic attack, agoraphobia, panic disorder, specific phobia, social phobia, obsessive compulsive disorder, posttraumatic stress disorder, acute stress disorder, generalized anxiety disorder, separation anxiety disorder, or substance-induced anxiety disorder; or the mood disorder is selected from bipolar disorders, depressive disorders selected from major depressive disorder, dysthymic disorder, or substance-induced mood disorder, or mood episodes selected from major depressive episode, manic episode, mixed episode, or hypomanic episode.

46. The method of claim 44 wherein the mammal is human.

47. A method for treating at least one neurodegenerative disorder in a mammal selected from Parkinson's disease, Huntingdon's disease, alzheimer's disease, amyotrophic lateral sclerosis, chronic dementia, or cognitive impairment comprising intranasally administering to a mammal in need thereof a therapeutically effective amount of the composition of claim 27.

48. The method of claim 47 wherein the mammal is a human.

49. A method for treating at least one condition in a mammal selected from inflammatory diseases; fibromyalgia; complications from herpes zoster; prevention of tolerance to opiate analgesia; or withdrawal symptoms from addictive drugs comprising intranasally administering to a mammal in need thereof a therapeutically effective amount of the composition of claim 27.

50. A method for treating pain in a mammal comprising administering intranasally to a mammal in need thereof a therapeutically effective amount of the composition of claim 27.

51. The method of claim 50 wherein the pain is at least one of neuropathic pain; cancer pain; visceral pain associated with pancreatitis or abdominal, pelvic or perineal regions; musculoskeletal pain associated with lower or upper back, spine, fibromylagia, temporomandibular joint, or myofascial pain syndrome; bony pain associated with bone or joint degenerating disorders; headaches; or pain associated with infections, sickle cell anemia, autoimmune disorders, multiple sclerosis, dental procedures, burns or inflammation.

52. The method of claim 50 wherein the mammal is human.

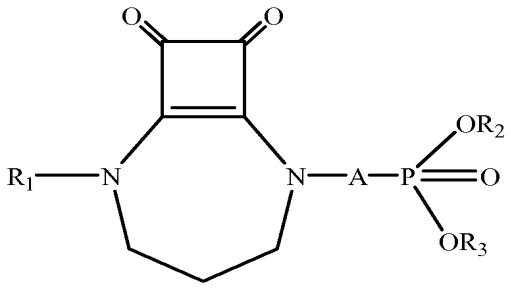
53. The method of claim 50 wherein the pain comprises neuropathic pain and is associated with at least one of diabetic neuropathy, peripheral neuropathy, post-herpetic neuralgia, trigeminal neuralgia, lumbar or cervical radiculopathies,

fibromyalgia, glossopharyngeal neuralgia, reflex sympathetic dystrophy, casualgia, thalamic syndrome, nerve root avulsion, or nerve damage cause by injury selected from phantom limb pain, reflex sympathetic dystrophy or postthoracotomy pain, cancer, chemical injury, toxins, nutritional deficiencies, or viral or bacterial infections.

54. The method of claim 50 further comprising administering a therapeutically effective amount of at least one pain relieving agent.

55. A pharmaceutical composition for intranasal administration, in unit dosage or multiple dose form, comprising:

a) a therapeutically effective unit dosage or multiple dose for intranasal administration of at least one compound of formula (I) or a pharmaceutically acceptable salt thereof:



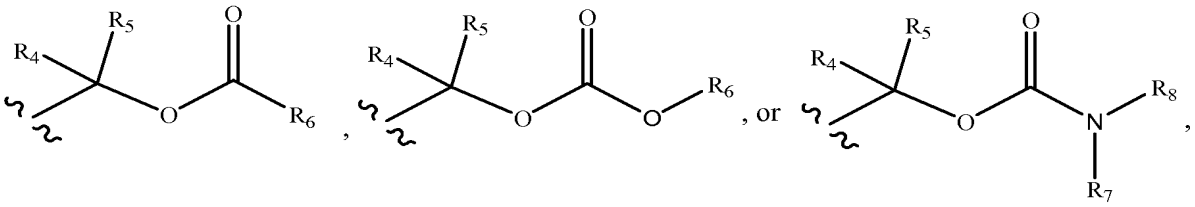
(I)

wherein:

R_1 is hydrogen, a C_1 to C_6 alkyl group, a C_2 to C_7 acyl group, a C_1 to C_6 alkanesulfonyl group, or a C_6 to C_{14} aroyl group;

A is alkylene of 1 to 4 carbon atoms or alkenylene of 2 to 4 carbon atoms;

R_2 and R_3 are independently selected from hydrogen, or



with the proviso that at least one of R_2 and R_3 is not hydrogen;

R_4 and R_5 are independently selected from hydrogen, a C_1 to C_4 alkyl group, a C_5 to C_7 aryl group, a C_6 to C_{15} alkylaryl group having 5 to 7 carbon atoms in the aryl ring, a C_2 to C_7 alkenyl group, or C_2 to C_7 alkynyl group, or R_4 and R_5 may together form a spiro C_3 to C_8 carbocyclic ring;

R_6 is a C_1 to C_{12} linear or branched alkyl group, a C_2 to C_7 linear or branched alkenyl or alkynyl group, a C_5 to C_{13} aryl group, a C_6 to C_{21} alkylaryl group having 5 to 13 carbon atoms in the aryl moiety; a 5 to 13 membered heteroaryl group, a 6 to 21 membered alkylheteroaryl group having 5 to 13 members in the heteroaryl moiety, a C_4 to C_8 cycloalkyl group, a C_5 to C_{16} alkylcycloalkyl group having 4 to 8 carbon atoms in the cycloalkyl ring;

R_7 and R_8 are independently selected from hydrogen, a C_1 to C_{12} linear or branched alkyl group, a C_2 to C_7 linear or branched alkenyl or alkynyl group, a C_5 to C_{13} aryl group, a C_6 to C_{21} alkylaryl group having 5 to 13 carbon atoms in the aryl moiety, a 5 to 13 membered heteroaryl group, a 6 to 21 membered alkylheteroaryl group having 5 to 13 members in the heteroaryl moiety, or R_7 and R_8 may together form a cycloalkyl or heterocycloalkyl group having in the ring 4 to 8 carbon atoms and optionally one to two atoms selected from nitrogen, oxygen or sulfur;

wherein any R_1 to R_8 group having an aryl, heteroaryl, cycloalkyl or heterocycloalkyl moiety may optionally be substituted on the aryl, heteroaryl,

cycloalkyl or heterocycloalkyl moiety with 1 to about 5 substituents independently selected from a halogen atom, a cyano, nitro or hydroxyl group, a C_1-C_6 alkyl group, or a C_1-C_6 alkoxy group; and

b) one or more pharmaceutically acceptable additives for forming a composition for intranasal administration.

56. The composition of claim 55 wherein at least one of the compound of formula (I) is selected from:

a) 3-{2-[8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl]ethyl}-3-oxido-7-oxo-7-phenyl-2,4,6-trioxa-3-phosphahept-1-yl benzoate;

b) 3-{2-[8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl]-ethyl}-3-oxido-7-oxo-8-propyl-2,4,6-trioxa-3-phosphaundec-1-yl 2-propylpentanoate;

c) 2,2-dimethyl-propionic acid {(2,2-dimethyl-propionyloxymethoxy)-[2-(8,9-dioxo-2,6-diaza-bicyclo[5.2.0]-non-1(7)-en-2-yl)-ethyl]-phosphinoyloxy} methyl ester;

d) 7-cyclohexyl-3-{2-[8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl]ethyl}-1,5-dimethyl-3-oxido-7-oxo-2,4,6-trioxa-3-phosphahept-1-yl cyclohexanecarboxylate;

e) 7-cyclohexyl-3-{2-[8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl]ethyl}-3-oxido-7-oxo-2,4,6-trioxa-3-phosphahept-1-yl cyclohexanecarboxylate;

f) [2-(8,9-Dioxo-2,6-diaza-bicyclo[5.2.0]non-1-(7)-en-2-yl)-ethyl]-phosphonic acid diisopropoxycarbonyl oxymethyl ester;

g) [2-[8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1 (7)-en-2-yl]ethyl]-phosphonic acid bis[1-(benzoyloxy)ethyl] ester;

h) benzoic acid [2-(8,9-dioxo-2,6-diaza-bicyclo[5.2.0]non-1(7)-en-2-yl)-ethyl]-hydroxy-phosphinoyloxymethyl ester; or

i) [2-(8,9-Dioxo-2,6-diaza-bicyclo[5.2.0]non-1(7)-en-2-yl)-ethyl]-phosphonic acid di- dimethylcarbamoyloxymethyl ester; or

a pharmaceutically acceptable salt thereof.

EVIDENCE APPENDIX

Copies of the following references were submitted by the Appellants and entered by the Examiner on September 6, 2006 as part of the response to the non-final Office Action mailed June 1, 2006:

- Wood PL.
  The NMDA receptor complex: a long and winding road to therapeutics.
  Drugs. 2005 Mar;8(3):229-35. Review.

- Heresco-Levy U.
  Glutamatergic neurotransmission modulators as emerging new drugs for schizophrenia.
  Expert Opin Emerg Drugs. 2005 Nov;10(4):827-44. Review.

- Bergink V, van Megen HJ, Westenberg HG.
  Glutamate and anxiety.
  Eur. Neuropsychopharmacol. 2004 May;14(3):175-83. Review.

- Parsons CG.
  NMDA receptors as targets for drug action in neuropathic pain.
  Eur J Pharmacol. 2001 Oct 19;429(1-3):71-8. Review.

- Brown DG, Krupp JJ.
  N-methyl-D-aspartate receptor (NMDA) antagonists as potential pain therapeutics.
  Curr Top Med Chem. 2006;6(8):749-70

- McCulloch J.
  Excitatory amino acid antagonists and their potential for the treatment of ischaemic brain damage in man.
  Br J Clin Pharmacol. 1992 Aug;34(2):106-14. Review.

RELATED PROCEEDINGS APPENDIX

No related appeals or interferences are pending.